**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Andrej BUGRIM et al.

Application No.: 10/518,103

Filed: (Int'l) June 18, 2003

For: METHODS FOR IDENTIFYING COMPOUNDS FOR TREATING DISEASE STATES

Confirmation No.: 5310

Art Unit: 1631

Examiner: K. Skowronek

**DECLARATION UNDER 37 C.F.R. § 1.132**

MS RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. I, Dr. Andrej Bugrim, Ph.D., am an expert in the field of systems biology and a named inventor of the present invention. I received my doctorate in chemistry from Brandeis University (Waltham, MA), after which I completed my post-doctoral training in nonlinear dynamics at the University of California at Davis (Davis, CA). Following completion of my formal training, I worked as a research associate at the Center for Computational Biology, Washington University School of Medicine (St. Louis, MO). Subsequently, I joined GeneGo, Inc. (St. Joseph, MI) as a Senior Scientist. I have been Chief Operating Officer of GeneGo, Inc. since 2002. My resume is attached hereto as documentation of my credentials (**Exhibit A**).

2. This Declaration is being filed in response to the Office's view, expressed in the final Office Action dated August 20, 2008 ("the OA"), that it would have been obvious to a person

skilled in the art to combine the teachings of Nakao *et al.* with those of Karp *et al.* and Kuffner *et al.* to arrive at the presently claimed invention (The OA at pages 6-9). The Office asserted:

> It would have been obvious to one of skill in the art to modify the method of reconstructing an organism's metabolism of Nakao et al. with the drug target identification of Karp et al. because Karp et al. shows that that integrated genome-metabolic pathways provide a framework for improved drug discovery. It would have been further obvious to modify the method of reconstructing metabolism with collected data of Nakao and the use of pathways to identify targets of Karp et al. with the DMD's of Kuffner et al. because Kuffner et al. shows DMD's allow the display of significant differences, to identify gaps in specific pathways and enable the interpretation of expression data by making predictions for proteins of unknown function and to propose the existence and/or absence of specific proteins or protein functions. (The OA at pages 8-9).

3. It is my understanding that evidence of secondary indicia of nonobviousness can be used to overcome an obviousness rejection if, *arguendo*, the Patent Office has showed sufficient evidence of *prima facie* obviousness. It is also my understanding that the secondary indicia of nonobviousness include, *inter alia*, the claimed invention's commercial success, a long-felt unresolved need in the industry, failure by others, skepticism by experts, and praise by others.

4. I hereby declare that, beginning in the early 1990s, the biomedical community sensed a growing need for integrating information on metabolic and other pathways and reconstructing biological processes in health and disease. Some of the most notable public projects in this area include the Kyoto Encyclopedia of Genes and Genomes (KEGG, cited in the OA), the Enzymes and Metabolic Pathways (EMP), the Biomolecular Interaction Network Database (BIND), BioCarta and EcoCyc. According to press releases issued at that time, tens of millions of dollars were invested in each of these projects. Even though these projects resulted in free, public-domain pathway analysis resources, they were unable to fully satisfy the needs of the scientific community in terms of reconstructing comprehensive organism- and condition-specific pathways and providing adequate tools for functional analysis of high-throughput molecular profiles. Some of the principal shortcomings of these public resources are:

(a) Lack of organism specificity, *i.e.*, data points from different organisms were pooled together, resulting in inconsistent and often incorrect pathways;

(b) Lack of comprehensive coverage, *i.e.*, most resources covered limited areas of cellular functionality but failed incorporate the full spectrum of biological processes;

(c) Inability to integrate heterogeneous information on metabolism and cell signaling with clinical and other phenotypical data; and

(d) Inability to combine pathways with high-throughput molecular data (*e.g.*, gene expression, proteomics, metabolomics)

5. I hereby declare that there have been multiple attempts by GeneGo's competitors to develop commercial tools that would allow analysis of high-throughput molecular data in the context of biological pathways and reconstruction of disease pathways. The list of private companies that have attempted to develop such software includes Informax, Inc. (acquired by Invitrogen Corp.; now part of Life Technologies Corp.), OmniViz, Inc. (acquired by BioWisdom Ltd.), Lion Bioscience Ltd. (acquired by BioWisdom Ltd.), Genedata AG and several others. None of these attempts have resulted in commercially successful products, and many of these companies have ceased to exist as independent entities.

6. I hereby declare that when GeneGo, Inc. applied for federal Small Business Innovation Research (SBIR) and Advanced Technology Program (ATP) funding in 2002 in order to create a commercial embodiment of the presently claimed invention, a number of expert reviewers expressed reservations that the project would not be feasible in view of the failed prior attempts by other companies and academic institutes.

7. I hereby declare that GeneGo, Inc. has successfully developed and marketed its flagship product, the MetaCore™ pathway analysis software, based on the presently claimed invention. Subsequently, additional products and services were developed and marketed that also utilize elements of the claimed invention. MetaCore™ was first marketed in 2004 and has so far generated approximately $14,000,000 in sales. MetaCore™ is now licensed to over 200 institutional customers with thousands of individual users. The list of customers includes virtually

every major pharmaceutical company, many mid-size and small biotech firms, over 50 major research universities and a number of U.S. Government agencies such as the National Institutes of Health (NIH), the Department of Defense (DOD), the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA). At the present time, approximately 50% of MetaCore™ customers are located in the U.S., 40% in Europe and 10% in Asia. Additionally, a number of "GeneGo Centers of Excellence" have been established at major universities, where use of MetaCore™ is now incorporated into the curriculum.

8. I hereby declare that, despite the availability of the above-mentioned public-domain resources free of charge starting in the mid-1990s, GeneGo, Inc. has been able to license its MetaCore™ product to hundreds of customers at rates ranging from $3000/year for an individual academic user to $500,000/year for a full commercial institutional license. Moreover, MetaCore™ has enjoyed annual sales growth rates of 40-60% since its release in 2004.

9. I hereby declare that MetaCore™ has received abundant praise from GeneGo, Inc.'s customers, partners and collaborators. A small sample of testimonials is reproduced below. A much longer list of testimonials may be found online at http://www.genego.com/testimonials.php.

> "We chose MetaCore™ as it has the most comprehensive, detailed database of human metabolism and signaling, and is also a one-stop shop for our systems analysis needs. Experimental data in nutrition are inherently complex, as the diet-influenced changes in disease onset and progression are subtle and multi-factorial. We also have the data from both human and model animals. In MetaCore™, we can upload and compare all these data on the same networks and pathways and then analyze the networks with a variety of tools." Dr. Ben van Ommen, Senior Research Fellow, Nutritional Systems Biology, TNO.

> "We spent quite some time evaluating systems biology platforms and were impressed by the depth and breadth of the MetaCore™ knowledge base." "MetaCore™ has impressive coverage of signaling and metabolic pathways and in-depth disease and tissue-specific data that is invaluable for our research. In addition, MetaCore™ has a flexible and powerful front-end that allows our bench scientists to integrate multiple data streams and algorithms to fully mine our bone therapy data." Dr. Daniel Chagnovich, Director of Research Operations, Velcura Therapeutics, Inc.

"MetaCore™ has grown to become a key component in the research toolbox in the life sciences, particularly within the pharmaceutical industry, and we are pleased to have the opportunity to work with GeneGo," commented Dr. Jonathan Sheldon, Chief Scientific Officer, InforSense Ltd.

"We see MetaCore™ as a further step into systems biology, a novel discipline which holds much promise for pharmaceutical research," said Dr. Friedrich Rippmann, Director of Bio- and Chemoinformatics at Merck KGaA.

"We were very pleased to work with the team at GeneGo on the identification of cattle orthologs. My group feels that MetaCore™ is currently the premier product for data mining and pathway analysis." Harris Lewin, Director of the Institute for Genomic Biology, University of Illinois at Urbana-Champaign.

"MetaCore™'s extensive information content allows us to perform detailed data analysis of high throughput assay results that is currently not possible with any other tool. MetaCore™ has been adopted as a favorite tool by our users from day one." Burak Kutlu, Ph.D., Research Scientist, Institute for Systems Biology.

10. I hereby declare that the success of MetaCore™ stems directly from the novel combination of elements recited in the presently claimed methods. Had this novel combination been obvious to a person skilled in the art at the time the invention was made, MetaCore™ would not have become the commercial and scientific success that it is.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Dated: January 21, 2009

Andrej Bugrim, Ph.D.

**EXHIBIT A**

## BIOGRAPHICAL SKETCH

| NAME | POSITION TITLE |
|---|---|
| Bugrim, Andrej, E | Chief Operating Officer |

**EDUCATION**

| INSTITUTION AND LOCATION | DEGREE *(if applicable)* | YEAR(s) | FIELD OF STUDY |
|---|---|---|---|
| Moscow State University, Moscow, Russia | *M.S.* | 1992 | Chemistry |
| Brandeis University, Waltham, MA | *Ph.D.* | 1997 | Chemistry |
| University of California, Davis, CA | *N/A* | 1997-1999 | NSF Training Program "Nonlinear Dynamics in Biology", Postdoctoral trainee |

**WORK EXPERIENCE**

1993-1997: Graduate Researcher/Teaching Assistant, Brandeis University, Waltham, MA;
1997-1999: Postdoctoral Trainee, Institute of Theoretical Dynamics, University of California, Davis, CA;
1999-2001: Research Associate, Center for Computational Biology, Washington University School of Medicine, St. Louis, MO;
2001-2002: Senior Scientist, GeneGo, Inc, Joseph, MI;
2002-present: Chief Operating Officer, GeneGo, Inc, St. Joseph, MI.

**HONORS**

1994-1995 Rosenberg Fellowship, Brandeis University
1995 Lakriz Fellowship, Brandeis University

**PROFESSIONAL ASSOCIATIONS**

2003-present Member, ISSX
2002-present Memebr, AAAS
2003-present Member, ISCB
2000-present Member, BioPathways Consortium

**PEER-REVIEWED PUBLICATIONS**

1. Beckman N, **Bugrim AE**, Zykov VS, Autowaves in polluted ecological systems, *Vestnik Moskovskogo Universiteta, Seriya 2 Khimiya* 1993, 34: 94-99.
2. **Bugrim AE**, Zhabotinsky AM, Epstein IR, Interference of crossing trigger waves in multilayer reaction-diffusion systems, *Phys. Rev. Lett.* 1995, 75: 1206-1209.
3. **Bugrim AE**, Zhabotinsky AM, Epstein IR, Mechanism for spontaneous formation of crossing chemical waves in a stratified reaction-diffusion system, *J. Phys. Chem.* 1995, 99: 15930-15933
4. **Bugrim AE**, Zhabotinsky AM, Epstein IR, Calcium waves in a model with a random spatially discrete distribution of $Ca^{2+}$ release sites, *Biophys. J.* 1997, 73(6): 2897-2906.
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10. Balakin KV, Ekins S, **Bugrim AE**, Ivanenkov YA, Korolev D, Nikolsky YV, Ivashchenko AA, Savchuk NP, Nikolskaya T, Quantitative structure-metabolism relationship of the metabolic N-dealkylation reaction rates, *Drug Metab. Dispos.* 2004, 32(10): 1111-1120.

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12. Ekins S, **Bugrim A**, Nikolsky Y, Nikolskaya T, Systems biology: applications in drug discovery, in: DRUG DISCOVERY HANDBOOK (Gad, S. ed., Wiley & Sons, 2005).

13. Nikolsky Y, Ekins S, Nikolskaya T, **Bugrim A**, A novel method for generation of signature networks as biomarkers from complex high-throughput data, *Tox. Lett.* 2005, 158: 20-29.

14. Nikolsky Y, Nikolskaya T, **Bugrim A**, Biological Networks and Analysis of Experimental Data in Drug Discovery, *Drug Discov. Today* 2005, 10(9): 653-662.

15. Ekins S, Andreyev S, Ryabov A, Kirillov E, Rakhmatulin EA, **Bugrim A**, Nikolskaya T, Computational prediction of human drug metabolism, *Expert Opin. Drug Metab. Toxicol.* 2005, 1(2): 303-324.

16. Ekins S, Andreyev S, Ryabov A, Kirillov E, Rakhmatulin EA, Sorokina S, **Bugrim A**, Nikolskaya T, A combined approach to drug metabolism and toxicity assessment, *Drug Metab. Dispos.* 2006, 34(3): 495-503.

17. Nikolsky Y, Ekins S, **Bugrim A**, Nikolskaya T, Pathway and networks analysis tools for high-throughput data, in: HIGH CONTENT SCREENING: A POWERFUL APPROACH TO SYSTEMS CELL BIOLOGY AND DRUG DISCOVERY (Humana Press, 2006).

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